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13. ABSTRACT (Maximum 200 words) The original purpose of the IDEA award was to recruit 36,000 additional runners to add to an existing cohort of 14,000 runners in order to create a total cohort of 50,000 who vigorously exercise. (Funding for surveillance was deferred to a future funding application.) We completed the design of the initial survey questionnaire and recruited the sample through direct mail solicitation of female running magazine subscribers and race participants. To date, we have received 31,647 questionnaires under DOD funding and should receive at least 1,800 of the additional 4,353 needed to achieve the target of 36,000 women runners. At least one mechanism for the protection of breast cancer is suggested by our baseline questionnaires. The onset of menopause (or amenorrhea) occurred significantly earlier in association with longer distances run per week. Cessation of periods was reported to occur 5 years earlier in women running 40 or more miles per week ( $39.5 \pm 10.2$ years) compared to those running less than 10 ( $44.43 \pm 8.54$ years). There was also a tendency (significant at $P < 0.0001$ ) for menses to have started about three months later in the higher mileage runners. The effect is however small compared to the apparent acceleration of menopause.					
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## Table of Contents

<b>Introduction</b>	<b>1</b>
<b>Body</b>	<b>1</b>
<b>Conclusions</b>	<b>6</b>
<b>References</b>	<b>7</b>
<b>Personnel</b>	<b>8</b>

**Introduction** Epidemiological studies suggest that regular exercise may reduce breast cancer risk. One hypothesis for this finding is that breast cancer risk increases with the cumulative number of ovulatory cycles. Strenuous physical exercise may reduce breast cancer risk by reducing the frequency of ovulatory cycles through delayed menarche, luteal suppression, oligomenorrhea, amenorrhea and/or accelerated menopause. To date, there have been no prospective studies of the association between strenuous physical activity and breast cancer.

Women who were athletically active in college are reported to have decreased breast cancer risk [1; 2]. Frish et al studied 2622 former college athletes and 2776 non-athletes [2]. The age-adjusted rates for breast cancer were 10.1/1000 for athletes and 15.6/1000 for nonathletes [2]. Bernstein et al [3] conducted personal interviews with a total of 545 women (aged 40 and younger at diagnosis) who had been newly diagnosed with in situ or invasive breast cancer and 545 control subjects in a case control study. After adjustment for potential confounding factors, they found that the average number of hours spent in physical exercise activities per week from menarche to 1 year prior to the case patient's diagnosis significantly predicted reduced breast cancer risk ( $P < .0001$  for trend). The odds ratio (OR) of breast cancer among women who, on average, spent 3.8 or more hours per week participating in physical exercise activities, was 0.42 (95% confidence limits = 0.27, 0.64) relative to inactive women. More recently, Rockhill et al found no relationship between strenuous exercise and breast cancer during 618,010 person years of follow-up in the Nurses Health Study II [4].

Factors that may reduce breast cancer risk in physically active women include delayed menarche (Early menarche is associated with increased breast cancer risk [5]. Delayed menarche is related to physical activity [2; 6]); short luteal phase (Physically active women often have very short cycles with presumably short, inadequate luteal phases [7], oligomenorrhea and secondary amenorrhea [8].) early menopause (Late menopause is reported to double the risk of breast cancer [9]. Earlier menopause has been reported for athletic, as compared to, non-athletic women [2].) and adiposity (Several studies report a positive association between upper body obesity and breast cancer [10; 11]. Athletic women have lower percent of body fat than non-athletic women.)

Whereas prior epidemiological studies on physical activity primarily focused on collegiate, occupational and leisure-time activities, the current study focuses on vigorous activity. Requiring continuous and sustained aerobic activity distinguishes running from occupational activity and many other sports. Our long-term objective is to test for a dose-response relation between distance run and breast cancer risk in 50,000 women runners. We will assess running level and other vigorous activities from questionnaires. This will be the first prospective study to concentrate on vigorous physical activity.

**Body** The purpose of the IDEA award is to recruit 36,000 additional runners to add to an existing cohort of 14,000 runners in order to create a total cohort of 50,000 who vigorously exercise, provide data on questionnaire validity and provide pilot data on surveillance. (Funding for surveillance will be deferred to a future funding application.) During the first year, we completed the design of the initial

survey questionnaire. Dr. Dee West, William Satariano, and Virginia Ernster reviewed the initial questionnaire and made a number of constructive comments. We revised and resubmitted the questionnaire to all three consultants, who recommended further changes. All three consultants approved the final form of the questionnaire. The approved questionnaire is presented in Figure 1.

We initially intended to include the survey in race packets distributed to runners by Runners' World magazine. Unacceptably low rates of return and high rates of cost per respondent (\$8.00) for these questionnaires precipitated a change in procedure. We therefore decided to obtain all of our questionnaires using direct mail solicitation. We purchased the names of 512,808 women runners from Runners' World magazine. This list includes the names of 378,147 women who participated in races during the last year, and 134,656 women who subscribe to Runner's World magazine. The first questionnaires were mailed in October, 1998. An additional 137,104 new questionnaires and 183,841 post cards were mailed in June of 1999, and 162,353 questionnaires were mailed to a subset of nonresponders from our first two mailings (zip code  $\leq 50000$ ) in September of 1999. The first mailing yielded 20,861 women, the second yielded an additional 5,986 women, and the third has to date yielded questionnaires from 4,800 women runners, and continues to be received. Thus we have received 31,647 questionnaires under DOD funding and should receive at least 1,800 of the additional 4,353 needed to achieve the target of 36,000 women runners. A more optimistic goal of 50,000 women runners, which was proposed in the first annual report, could not be recruited within the funding level provided by the IDEA award.

We utilized electronic TIFF files to create a system that digitally archives the questionnaires as they arrive. We used a 20 ppm duplex document scanner to image forms with one-pass, double-sided scanning. The scanner supports scanning resolutions up to 300 dpi and is equipped with an automatic document feeder that holds up to 100 pages for unattended scanning. We used Alchemy software from IMR to organize the digitized questionnaires and to create self-contained, high performance databases on low-cost, recordable CDs. The software enables us to browse, search and retrieve individual, hand-written questionnaires using a CD-ROM reader. The software provides highly compressed full-text indices, fast retrieval from large databases, profile field query, and high-performance document viewers. All 26,841 questionnaires received through August of this year have been scanned.

The participant's name and address were printed directly on each questionnaire. The software reads these data and the participant's ID number directly off the questionnaire using optical character recognition. Inclusion of the participant name and address in the database by scanning has reduced manual data entry cost. The system stores the names and addresses of the participant's contacts as images and will print them directly as hand written address labels when required, also reducing data entry cost. Back-up copies of these data bases are stored within our offices in secured media vaults (fire protection rating of 125 degrees for 1 hour @1700 degrees). The software and media storage safe provide insurance against catastrophic loss of the questionnaires.

# National Runners' Health Study Questionnaire

1. Birthdate (mo/day/yr): \_\_\_\_\_ / \_\_\_\_\_ / \_\_\_\_\_
2. Sex (write number): 1) male 2) female ....
3. Race (write number): 1) White 2) Hispanic 3) Black 4) Native-American 5) Asian/Pacific Is. 6) Other ..
4. Years of education (examples: HS = 12; B.S. or B.A. = 16; M.S. or M.A. = 18; Ph.D. or M.D. = 20) .....
- 5-9. Average miles run each week for: 1995 \_\_\_\_\_ 1996 \_\_\_\_\_ 1997 \_\_\_\_\_ 1998 \_\_\_\_\_ 1999 \_\_\_\_\_
10. During your usual run, how many minutes does it take for you to run one mile? .....
11. At what age did you most recently start running 12 or more miles per week? .....
12. What was your weight when you most recently started running 12 or more miles per week? .....
13. What was your best 10-K time between 1995 and 1999 (leave blank if never run)? .....
14. How many marathons did you run between 1995 and 1999 (write zero if none)? .....
15. What was your best marathon time between 1995 and 1999? .....
16. How many hours per week do you train for events that are 400 meters or less (write zero if none)? .....
17. During an average week, how many miles is your longest run? .....
18. During an average week, how many minutes do you spend stretching (write zero if none)? .....
19. How many times per week do you run or do comparably vigorous exercise? .....
20. During the last 3 months, how many days have you had to curtail your running due to injury? .....
21. When you were in high school, how physically active were you compared with other students of the same gender? 1) less active; 2) average; 3) more active; 4) much more active .....
22. What is your current height (in inches, without shoes)? .....
23. What is your current weight (in pounds, pre-pregnancy weight if pregnant)? .....
24. What is the most you have ever weighed (excluding pregnancies)? .....
25. How old were you when you weighed the most? .....
26. Do you have a twin (write number)? 0) no; 1) yes-fraternal; 2) yes-identical .....
27. If you have ever had a heart attack, please give your age when it occurred (leave blank if never). ....
28. Do you currently smoke cigarettes? 1) no-never smoked; 2) no-ex-smoker; 3) yes-current smoker ....
29. How many cigarettes per day were you smoking when you last smoked? .....
30. How many total years had (have) you smoked (write zero if none)? .....
31. If you are an ex-smoker, how old were you when you quit (leave blank if not ex-smoker)? .....
32. During an average week, how many 4-oz. glasses of wine do you drink (write zero if none)? .....
33. During an average week, how many 12-oz. bottles of beer do you drink (write zero if none)? .....
34. During an average week, how many mixed drinks or liqueurs do you drink (write zero if none)? .....
35. During an average week, how many milligrams (mg) of vitamin C supplement do you take (write zero if none)? .....
36. During an average week, how many milligrams (mg) of vitamin E supplement do you take (write zero if none)? .....
37. During an average week, how many milligrams (mg) of calcium supplement do you take (write zero if none)? .....
38. During an average week, how many aspirin tablets do you take (write zero if none)? .....
39. During an average week, how many servings of beef, lamb or pork do you eat (write zero if none)? .....
40. During an average week, how many servings of fish do you eat (write zero if none)? .....
41. During an average week, how many pieces of fruit do you eat (write zero if none)? .....
42. Are you one of the following: 1) lacto-vegetarian; 2) strict vegetarian; 3) not vegetarian .....
43. Women: a) At what age did you have your first menstrual period? .....
- b) Do you currently have menstrual periods? 1) no; 2) yes; 3) not sure .....
- c) If yes, how long is your usual cycle? (days from start of period to start of next period) .....
- d) If you are no longer having menstrual periods, at what age did you stop? .....
- e) How many total years have you used oral contraceptives (write zero if none)? .....
- f) What age did you have your first full term pregnancy (leave blank if never)? .....
- g) How many children have you had (write zero if none)? .....
- h) How many total months have you breast fed (all pregnancies combined, write zero if never? .....
- i) Has your uterus been removed? 1) no; 2) yes, removed; 3) unsure .....
- j) Have your ovaries been removed? 1) no; 2) one removed; 3) both removed; 4) unsure .....

44. Please provide, to the best of your ability, your body circumference in inches and bra cup:

	Now	At greatest weight	When started running	At 18 years old
Chest (men and women):	_____	_____	_____	_____
Waist (men and women):	_____	_____	_____	_____
Hips (men and women):	_____	_____	_____	_____
Bra cup (women only):	_____	_____	_____	_____



## The National Runners' Health Study needs your help

By completing this questionnaire, you will be participating in an important research project which will test whether running prevents heart disease and breast cancer. **If you wish to take part in this important study, please complete the questionnaire, sign, and date below.** Send your research questionnaire to Paul Williams, Ph.D., Lawrence Berkeley National Laboratory, Bldg. 934, Berkeley, CA 94720. Our toll-free telephone number is (800) 782-6817. You must be at least 18 years old to participate. This research is funded in part by the United States government, including the National Institutes of Health and the Department of Defense.

45. Telephone: (     ) \_\_\_\_\_
46. Birthdate (mo/day/yr): \_\_\_\_\_
47. Country of birth: \_\_\_\_\_
48. Social Security number: \_\_\_\_\_  
(to identify deaths on National Death Index)
49. E-mail address: \_\_\_\_\_
50. Do you currently take medications? (write numbers)  
0) none; 1) drugs for blood pressure; 2) drugs for thyroid; 3) drugs for cholesterol; 4) drugs for diabetes;  
5) oral contraceptives; 6) estrogen only; 7) estrogen plus progesterone; 8) other female hormone replacement;  
9) nonaspirin pain relief medication \_\_\_\_\_  
Please provide product name and daily dose \_\_\_\_\_
51. If you, your biological parents, full siblings, or children ever had cancer, please provide the following:  
a) relationship: \_\_\_\_\_; site: \_\_\_\_\_; age when diagnosed: \_\_\_\_\_  
b) relationship: \_\_\_\_\_; site: \_\_\_\_\_; age when diagnosed: \_\_\_\_\_  
c) relationship: \_\_\_\_\_; site: \_\_\_\_\_; age when diagnosed: \_\_\_\_\_
52. How many full brothers and sisters do you have? \_\_\_\_\_ brothers: \_\_\_\_\_; sisters: \_\_\_\_\_
53. On average how many hours per week do you spend: running \_\_\_\_\_ cycling \_\_\_\_\_ swimming \_\_\_\_\_  
other exercise (describe) \_\_\_\_\_
54. Please give us the names of 2 people who will know of your whereabouts for the next 10 years.  
Name: \_\_\_\_\_  
Address: \_\_\_\_\_  
City, state, zip: \_\_\_\_\_  
Telephone: (     ) \_\_\_\_\_ (     ) \_\_\_\_\_

55. Informed Consent: By signing below, I agree to the following: I understand that my participation in this research is completely voluntary and that I need not take part. I understand that I will be contacted at a future date in order to determine my health status and interest in related health studies, and that the researchers may find out whether I have had cancer or died through national health registries. I understand that nothing in this consent form is a waiver or release of my legal rights. I understand that the information provided to the National Runners' Health Study will be used for statistical purposes only and will remain confidential to the extent allowed by law. In the unlikely event of an investigation into the conduct of this research project the funding agencies may have access to my research record. I understand that I can stop participating in this study at any time, but that I cannot withdraw any information already submitted. I understand that if I suffer an injury as a direct and proximate result of participating in this study by filling out this survey or by supplying my medical information, medical care will be available to me. The cost of this care will be paid by the Regents of the University of California, pursuant to its contract with the United States Department of Energy. If you have any questions regarding this assurance, you may consult the Committee for Protection of Human Subjects, A & E Building, University of California, Berkeley CA 94720-1340; 510/642-7461.

Signature: \_\_\_\_\_ Date: \_\_\_\_\_

56. **(Very important but optional)** Permission to Release Medical Information: I hereby grant permission for the release of the following medical information to Paul Williams, Ph.D., who is conducting the National Runners Health Study: height, weight, cholesterol (total, HDL, LDL, VLDL), triglycerides, blood pressure, heart rate, uric acid, fasting glucose, and white blood-cell count.

Signature: \_\_\_\_\_ Date: \_\_\_\_\_

Name of primary care physician (print clearly): \_\_\_\_\_  
Address: \_\_\_\_\_  
City, state, zip: \_\_\_\_\_  
Telephone (if known): \_\_\_\_\_



Table 1. Characteristics of 26,847 female runners whose data has been entered

	0-9 mi/week 4772	10-19 mi/week 7924	20-29 mi/week 7483	30-39 mi 4070	≥ 40 mi/week 2598	P
Sample size (entered)						
Age (years)	40.87 ± 11.42	40.31 ± 10.18	39.92 ± 9.84	38.71 ± 10.15	36.91 ± 10.47	.001
Education (years)	16.02 ± 2.47	16.20 ± 2.29	16.20 ± 2.29	16.07 ± 2.32	16.05 ± 2.32	.001
Running speed (min/mi)	9.91 ± 2.76	9.42 ± 1.72	8.95 ± 1.29	8.65 ± 1.25	8.19 ± 1.01	.001
Longest run (mi)	5.05 ± 3.31	5.71 ± 3.12	7.80 ± 3.26	9.74 ± 3.46	12.15 ± 4.48	.001
Marathon time (min)	269.16 ± 44.87	274.92 ± 39.66	261.98 ± 37.91	249.80 ± 36.10	227.15 ± 34.36	.001
Marathons (# since 1995)	0.49 ± 1.98	0.49 ± 2.24	1.19 ± 2.73	2.04 ± 4.04	3.34 ± 4.97	.001
Time 10 km (min)	54.16 ± 12.08	53.32 ± 9.96	50.71 ± 8.40	48.18 ± 7.65	44.51 ± 6.79	.001
Age started running	31.15 ± 11.38	32.07 ± 10.47	30.10 ± 10.25	27.94 ± 9.76	24.94 ± 9.96	.001
Years run	9.49 ± 8.35	8.16 ± 7.46	9.84 ± 7.77	10.73 ± 7.18	11.96 ± 7.66	.001
Days injured	8.04 ± 21.55	5.57 ± 15.60	5.03 ± 14.09	5.09 ± 13.32	5.81 ± 14.55	.001
Anaerobic training (h/wk)	0.45 ± 2.45	0.39 ± 2.84	0.51 ± 2.49	0.84 ± 3.94	0.91 ± 4.82	.001
Running (h/week)	2.59 ± 3.03	3.56 ± 2.71	5.05 ± 3.96	6.51 ± 5.25	8.04 ± 5.04	.001
Cycling (h/week)	0.79 ± 2.53	0.77 ± 2.11	0.84 ± 2.13	0.99 ± 2.21	1.19 ± 2.73	.001
Swimming (h/week)	0.34 ± 2.07	0.29 ± 1.33	0.35 ± 1.52	0.42 ± 1.43	0.48 ± 1.13	.001
Vigorous exercise (times/wk)	3.98 ± 2.72	4.54 ± 2.26	5.15 ± 2.12	5.68 ± 2.69	6.33 ± 2.25	.001
Age menses	12.90 ± 1.56	12.89 ± 1.52	12.93 ± 1.49	13.03 ± 1.57	13.14 ± 1.75	.001
Age menopause	44.43 ± 8.54	43.81 ± 8.46	43.19 ± 8.97	42.31 ± 9.53	39.46 ± 10.16	.001
Age first pregnancy	26.01 ± 5.12	26.04 ± 5.00	25.99 ± 5.04	25.88 ± 4.94	25.92 ± 5.08	.88
Cycle length (days)	28.21 ± 3.19	28.12 ± 3.19	28.13 ± 3.25	28.24 ± 3.27	28.54 ± 3.86	.005
Children (number)	1.28 ± 1.83	1.22 ± 1.48	1.26 ± 2.13	1.07 ± 1.54	0.91 ± 1.48	.001
Oral contraceptives (years)	5.14 ± 5.54	5.43 ± 5.51	5.30 ± 5.50	5.11 ± 5.58	4.25 ± 5.04	.001
Breast fed (months)	6.82 ± 13.94	6.90 ± 13.15	7.18 ± 13.39	6.26 ± 13.98	5.73 ± 12.48	.001
Height (inches)	64.81 ± 2.83	64.95 ± 2.76	64.89 ± 2.71	64.95 ± 2.78	64.85 ± 2.68	.11
Body mass index (kg/m <sup>2</sup> )	22.51 ± 3.22	22.04 ± 2.76	21.48 ± 2.35	21.04 ± 3.09	20.51 ± 1.97	.001
Waist to hip ratio	0.77 ± 0.10	0.77 ± 0.18	0.77 ± 0.19	0.76 ± 0.13	0.77 ± 0.08	.24
Red meat (servings/week)	2.26 ± 2.51	2.33 ± 2.38	1.79 ± 2.48	1.57 ± 2.10	1.39 ± 1.97	.001
Fruit (servings/week)	9.00 ± 6.58	9.68 ± 6.83	10.42 ± 7.10	10.50 ± 7.22	11.31 ± 7.92	.001
Fish (servings/week)	1.16 ± 1.25	1.15 ± 1.31	1.18 ± 1.34	1.24 ± 1.53	1.19 ± 1.46	.03
Alcohol (oz/week)	1.38 ± 1.98	1.53 ± 4.40	1.51 ± 2.01	1.46 ± 2.16	1.28 ± 2.04	.004
Calcium (g/week)	1.65 ± 3.82	1.66 ± 3.27	1.78 ± 3.88	1.69 ± 4.14	1.71 ± 3.93	.42
Vitamin C (g/wk)	1.47 ± 3.57	1.68 ± 4.51	1.78 ± 4.66	1.76 ± 3.57	1.92 ± 4.64	.002
Vitamin E (100xIU/day)	127.17 ± 430.66	120.91 ± 262.16	134.09 ± 412.88	124.97 ± 303.04	130.28 ± 411.67	.36
Years smoked	3.31 ± 7.02	3.43 ± 8.27	3.44 ± 20.26	2.81 ± 5.97	4.06 ± 79.33	.61

The initial IDEA award did not budget funds for data entry. Nevertheless, we have been able to organize, check, and enter the data for 26,847 women recruited through August 1999. Their data appear in Table 1 of this report.

At least one mechanism for the protection of breast cancer is suggested by our baseline questionnaires. Table 1 shows that the onset of menopause (or amenorrhea) occurred significantly earlier in association with longer distances run per week. Cessation of periods was reported to occur 5 years earlier in women running 40 or more miles per week ( $39.5 \pm 10.2$  years) compared to those running less than 10 ( $44.43 \pm 8.54$  years). The younger survey age of the higher mileage runners (see Table 1) did not explain this association. Specifically, using age as the time variable, the Cox proportional hazard model (survival analysis) showed that mileage was significantly associated ( $P < 0.0001$ ) with age of menopause when premenopausal women were censored at their survey age.

There was also a tendency (significant at  $P < 0.0001$ ) for menses to have started about three months later in the higher mileage runners. The effect is however small compared to the apparent acceleration of menopause. The modest difference in menses may reflect a somewhat more active adolescence, since higher-mileage runners were more likely to recall being more active during high school than lower mileage runners.

Table 1 distinguishes other characteristics of the 26,847 women by running distance. Running greater distances per week was associated with younger age, faster usual running speed during usual runs, marathons and 10 km races. Higher mileage runners were more likely to engage in other vigorous activities including cycling and swimming. They tend to consume more vitamin C, more fruit, and less red meat. Higher mileage runners spent fewer months breast feeding and using oral contraceptives. These presumably reflect the inverse association between age and mileage.

**Conclusion** Thus, in terms of the statement of work, we have created a survey questionnaire that represents the consensus of the principal investigator and consultants, we have identified a target population of over one-half million female runners, and we have established a system for archiving the questionnaires as they arrive. We believe that we have been successful in creating a very large cohort for the study of breast cancer in an epidemiological study of runners. We expect to recruit 36,000 women runners as specified in the original IDEA grant.

During the next funding cycle, we will request funding for breast cancer surveillance under a regular type research grant. We believe that this is warranted because: 1) the study is unique in its focus on vigorous exercise; 2) the large size of the cohort provides substantial statistical power to accept or reject the hypothesis that vigorous exercise reduces breast cancer; and 3) the baseline questionnaire provides preliminary evidence for one plausible mechanism for reducing risk by exercising vigorously.

## References

- [1] Frish RE, Wyshak G, Albright NL, et al. Lower prevalence of breast cancer and cancers of the reproductive system among former college athletes compared to nonathletes. *Br. J. Cancer* **52**: 885-891, 1985.
- [2] Frish RE, Wyshak G, Albright NL, Albright E, Schiff I, Witschi J, Marguglio M. Lower lifetime occurrence of breast cancer and cancers of the reproductive system among former college athletes. *Am J Clin Nutr* **45**: 328-335, 1987
- [3] Bernstein L, Henderson BE, Hanisch R, et al. Physical exercise and reduced risk of breast cancer in physically active women. *J Natl. Cancer Institute*. **86**: 1403-1408, 1994
- [4] Rockhill B, Willett WC, Hunter DJ, Manson JE, Hankinson SE, Spiegel,an D, Colditz GA. Physical activity and breast cancer risk in a cohort of young women. *J Natl Cancer Inst* 1998, **90**:1155-1160
- [5] Pike MC, Hendersen BE, Casagrande JT. Epidemiology of breast cancer as it relates to menarche, pregnancy and menopause. In Pike MC, Siiteri PK, Welsch CW et al. *Hormones and breast cancer. Banbury report 8.* Cold Springs Harbor, NY Cold Spring Harbor Laboratory 1981: 3-18.
- [6] Merzenich H, Boeing H, Wahrendorf J. Dietary fat and sports activity as determinants for age at menarche. *Am J Epidemiol* **138**: 217-224, 1993
- [7] Bernstein L, Ross R, Lobo RA, et al. The effects of moderate physical activity on menstrual patterns in adolescence: implications for breast cancer prevention. *Br J Cancer* **55**: 681-683, 1987
- [8] Frish RE, Gotz-Welbergen AV, McArthur JW, et al. Delayed menarche and amenorrhea of college athletes in relation to age of onset of training. *JAMA* **246**:1559-1563, 1981
- [9] Feinleib M. Breast cancer and artificial menopause: a cohort study. *J Nat Cancer Institute* **41**: 315-329, 1968
- [10] Schapira DV, Kumar NB, Lyman GH, Cox CE. Abdominal obesity and breast cancer risk. *Ann Int Med* **112**: 182-186, 1990.
- [11] Ballard-Barbash R, Schatzkin A, Carter CL, Kannel WB, Kreger BE, D'Agostino RB, Splansky GL, Anderson KM, Helsel WE. Body fat distribution and breast cancer in the Framingham Study *J Natl Can Instit.* **82**: 286-290, 1990.

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